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A REVIEW OF INFORMATION ON NORNICOTINE

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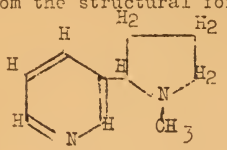
Introduction

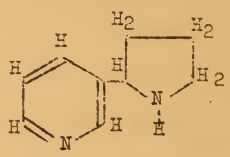
Nornicotine is a liquid alkaloid, closely related to nicotine both in chemical structure and in physiological behavior. It occurs in ordinary tobacco, Nicotiana tabacum L., in other species of Nicotiana, and in at least one other plant as well, viz, Duboisia hopwoodii F. Muell.

Nornicotine is an alkaloid of relatively recent history. The word nornicotine, which means the normal or parent form of nicotine, apparently first occurred in chemical literature in 1879 when Andreoni (3a) attempted to make it from nicotine by the action of hydrochloric and hydriodic acids. Pictet and Rotschy (30) in 1901 also referred to nornicotine. The first actual claim for its existence appeared in 1927 on the part of M. and N. Polonovski (32,33), who described a method for preparing various nor-alkaloids, of which nornicotine was one. In 1928 Ehrenstein (10, 11) reported finding it in tobacco. In 1930 Von Braun and Weissbach (5) obtained it by demethylating nicotine. Since then a number of papers dealing with nornicotine have appeared. The most important contributions have been made by Späth and coworkers (38 to 46), who have greatly elaborated the entire field of tobacco alkaloids.

The relationship between nicotine, $C_{10}H_{14}N_2$, and nornicotine, $C_9H_{12}N_2$, is seen from the structural formulas.



Nicotine



Nornicotine

Where nicotine has a methyl group joined to the pyrrolidine-nitrogen atom, nornicotine has a hydrogen atom. The latter alkaloid is therefore a secondary-tertiary base, in distinction from nicotine, which is ditertiary. Because of its secondary character nornicotine enters into a number of reactions which are not possible for nicotine. A more descriptive name for nornicotine is beta-pyridyl-alpha-pyrrolidine, or 2-(3'-pyridyl)pyrrolidine.

Nornicotine, like nicotine, is optically active. All three forms, d-, l-, and dl-, occur in nature and have also been synthesized.

The most prominent source of nornicotine, from the standpoint of present available supply, is ordinary tobacco, Nicotiana tabacum. The proportion of nornicotine in the total alkaloids is variable; in most strains the percentage is low, being of the order of a few percent, but it can also occur in quantities up to 95 percent of the total alkaloids. The latter case is apparently connected with low-nicotine tobaccos. The l-form is the principal isomer occurring in tobacco, but the dl-form also occurs.

N. silvestris Speg. and Comes is a plant also containing a notable quantity of the l-form of nornicotine, which is usually the predominating alkaloid therein. Other species of Nicotiana no doubt contain this alkaloid, but for the most part their alkaloidal nature has not been completely investigated.

Both d-nornicotine and dl-nornicotine occur in the Australian plant Duboisia hopwoodii.

Physical Properties

Nornicotine is a colorless, hygroscopic, somewhat viscous liquid with a slight amine odor which is definitely less pungent than the odor of nicotine. It appears to be more stable than nicotine, as it colors only moderately (yellow) in a clear-glass bottle exposed to light, and with access to air. It is miscible with water and organic solvents in all proportions. Strong alkali causes it to separate from aqueous solutions.

It is only slightly volatile with steam, in which respect it differs from nicotine, which is readily volatile. This difference has been utilized in separating the two bases.

The picrate of nornicotine is more soluble than that of nicotine, a difference which has also served in the separation of these bases.

The most trustworthy values of the physical properties of nornicotine have been selected from the literature and are recorded below. Although such properties do not usually vary with optical isomers, the nature of the isomer is noted with the value cited. The values for nicotine are also recorded, for comparison.

Specific gravity

$d_4^{19.5}$ = 1.0737 (Ehrenstein, 13). l and dl.

d^{20} = 1.07 (Smith, 37). l.

d^{23} = 1.070 (Späth and Zajic, 46). l.

d^{20} = 1.070 (Späth, Marion, and Zajic, 45). l.

d^{17} = 1.0757 (Hicks and LeMessurier, 18). d and dl.

d^{20} = 1.072 (Späth, Hicks, and Zajic, 39). d.

Nicotine, d_4^{20} = 1.0092.

Boiling point

130.5-131.3° at 11 mm. (Ehrenstein, 13). l and dl.
134-135° at 14 mm. (Ehrenstein, 13). l and dl.
139-140° at 12 mm. (Craig, 7). dl.
139-140° at 12 mm. (von Braun and Weissbach, 5). l and dl.
266-267° at atm. pres. (von Braun and Weissbach, 5). l and dl.
270-271° at atm. pres. (Smith, 37). l.
266-268° at atm. pres. (Hicks and LeMessurier, 18). d and dl.
117° at 4.35 mm. (Hicks and LeMessurier, 18). d and dl.
117° at 3.6 mm. (Späth, Hicks, and Zajic, 38). d and dl.
Nicotine, 246° at 745 mm.; 124° at 23 mm.

Refractive index

$N_D^{18.5}$ = 1.5378 (Ehrenstein, 13). l and dl.

$N_D^{18.6}$ = 1.5490-1.5518 (Hicks and LeMessurier, 18). d and dl.

$N_D^{18.3}$ = 1.5490 (Späth, Hicks, and Zajic, 38). d and dl.

Nicotine, n_D^{15} = 1.5300.

Optical rotation

$[alpha]_D^{23}$ = -88.8° (Späth and Zajic, 46). l.

$[alpha]_D^{20}$ = +86.3° (Späth, Hicks, and Zajic, 39). d.

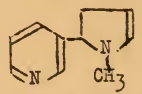
Nicotine, $[alpha]_D^{20}$ = -169.3°.

Ultra-violet absorption

Maximum at 2600 A.U.; log e = 3.15 (Hicks and LeMessurier, 18). d and dl.
Nicotine, maximum at 2604 A.U.; log e = 3.37.

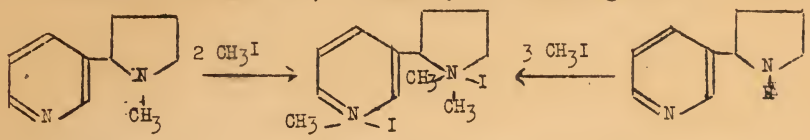
Occurrence

Ehrenstein (10, 11) in 1928 presented preliminary results of an investigation of the secondary alkaloids of tobacco. A further statement (12) appeared in 1930, and in 1931 (13) a complete account of his work appeared. He reported the finding of two new alkaloids in tobacco, one of which was l-nornicotine.

The existence in tobacco of alkaloids other than nicotine goes back to Pictet and Rotschy (30), who in 1901 reported finding three new alkaloids. One of these was called "nicoteine", b. p. 266-7°; the formula $C_{10}H_{12}N_2$ and structure  were assigned to it.

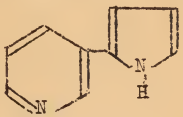
Noga (28) in 1914 confirmed the presence of this body. Ehrenstein, however, doubted the purity of "nicoteine" and reinvestigated the matter. He readily obtained a fraction of alkaloids, b. p. 269-70°, which corresponded well with nicotcine. A methylimino ($N-CH_3$) determination was negative, however, and nence the structure assigned above was incorrect. He found that both from the steam-volatile and the nonvolatile portions of the original tobacco extract this fraction of alkaloids could be isolated. After several fractionations of the crude base by distillation, the picrate was precipitated and then fractionally crystallized from different solvents. In this way two different picrates were obtained, a higher-melting one corresponding to a higher-boiling alkaloid and a lower-melting one corresponding to a lower-boiling alkaloid. The former of these is not considered here, except to note that he concluded it was anabasine, which was an error, as Späth and Kesztler (42) later showed it was anatabine.

The lower-boiling alkaloid was found to be l-nornicotine, $C_9H_{12}N_2$, b. p. 130.5-131.3° (11 mm.) or 134-5° (14 mm.), $d_4^{19.5}$ = 1.0737, $[\alpha]_D^{20}$ = -17.70°, $N_D^{18.5}$ = 1.5378. It was a nearly colorless liquid of a slight amine odor, which hardly colored after 1 year in a sealed tube. The HCl salt was dextrorotatory. Oxidation with HNO_3 gave nicotinic acid; the $N\text{-}CH_3$ determination showed absence of alkylated nitrogen. The methiodide derivative made from it was identical in properties with the corresponding derivative made from nicotine, as shown by the following scheme:



Nicotine (HI formed in the case of nornicotine) Nornicotine

Other compounds made to characterize the base were: picrate, m. p. 191-2°; picrolonate, m. p. 250-2°, urea, m. p. 167-70°; phenylthiourea, m. p. 176-7°. The natural l-nornicotine isolated here agreed well in properties with that already reported by von Braun and Weissbach (5), which was made by demethylating nicotine. Ehrenstein quantitatively dehydrogenated nornicotine over Pt-asbestos at 320-30° to 2-[beta-pyridyl]-pyrrole, or nornicotyrine,



, m. p. 100-102°, picrate m. p. 202-3°. By this investigation Ehrenstein proved for the first time the presence of nornicotine in tobacco.

Shmuck (35) in 1934 published results on the investigation of several species and hybrids of Nicotiana. The chief feature was the attempt to characterize the several types by division into steam-volatile and nonvolatile alkaloids. The following table illustrates the character of the data in the paper.

Plant	Total alkaloid content	Alkaloids	
		Volatile	Nonvolatile
	Percent	Percent	Percent
Nicotiana alata Link and Otto	0.1130	0.0	100.0
N. longiflora Cav.	.0766	0.0	100.0
Petunia violacea Lindl.	.1201	0.0	100.0
N. glauca Graham	.4774	23.8	76.2
N. silvestris Speg. and Comes	.5577	11.8	88.2
N. glutinosa L.	.3342	0.6	99.4
N. tabacum L.	1.94	100.0	0.0
N. tabacum x N. silvestris	.91	24.6	75.4
N. tabacum x N. glauca	.19	80.0	20.0

The division of alkaloids into volatile and nonvolatile groups has a bearing on their nature in that nicotine is readily volatile with steam while the other tobacco alkaloids are much less volatile, although still volatile enough on prolonged distillation to be detected in the distillate. The above table shows complete volatility of the alkaloid of N. tabacum, which is indicative of nicotine only. The first three plants, of minor interest here, have completely nonvolatile alkaloids; their study may be interesting in other connections. Three species, N. glutinosa, N. silvestris, and N. glauca, are of great interest because of their high total alkaloid content and their high proportion of nonvolatile alkaloid.

Shmuck did not positively identify any of the alkaloids except nicotine. However, in the following table, which gives the melting points of the picrates of the volatile alkaloids, some insight is gained into their character.

Volatile alkaloid of--	Picrate, m. p.
Nicotiana glauca Graham	207-8°
N. silvestris Speg. and Cones	176-8°
N. glutinosa L.	208-10°
N. tabacum L.	218-9°
N. tabacum x N. glauca	198-200°
N. tabacum x N. silvestris	178-80°

The lowest-melting picrate of the group nicotine, nornicotine, and anabasine is that of nornicotine (m. p. 191-2°); hence N. silvestris (Smith, 37), as well as the hybrid N. tabacum x N. silvestris, contains nornicotine as the chief volatile alkaloid constituent. The alkaloids of N. glauca and of N. glutinosa, forming picrates of closely agreeing melting points, are obviously alike. Smith (36) later showed that the alkaloid of N. glauca is largely anabasine, and this alkaloid has since been reported in N. glutinosa by H. H. Smith and C. R. Smith (unpublished).

Späth and Zajic (46) in 1935, in the third of a series of papers on tobacco alkaloids, reported on the isolation of l-nornicotine therein. Starting with a mixture of Kentucky and Virginia tobacco, they prepared a concentrated extract, which was made strongly alkaline and exhaustively extracted with ether. The ether extract was fractionally distilled, giving a main fraction distilling at 94-5° (1 mm.) and a higher-boiling fraction. The ether solution of the main fraction was fractionally extracted with a saturated NaCl solution containing a small quantity of HCl. Each fraction was made alkaline and steam-distilled under vacuum at low temperature until all the nicotine was expelled. The alkaloid recovered from the residue was converted into picrate (m. p. 184-8°), and the base, still not pure, was recovered and distilled (1 mm.). There was thus obtained an almost colorless liquid having a specific rotation $[\alpha]_D^{22} = -39.7°$. This crude nornicotine was purified by crystallization as the perchlorate from methanol-ether solution in the form of white crystals. The free base recovered from the perchlorate had, after distillation at 1 mm., a specific rotation of $[\alpha]_D^{23} = -88.8°$ (the density calculated therefrom is $d_4^{23} = 1.070$). Analysis for carbon and hydrogen agreed with the composition $C_9H_{12}N_2$. The picrate melted at 191-2°, and the melting point of a mixture of this picrate with the picrate of the Duboisia base (38), which was a mixture of d- and dl-[illegible]cotine, showed

no depression. The l-nornicotine was methylated with formaldehyde and formic acid into a base which agreed in properties with those of l-nicotine, as shown by optical rotation and by the melting points of the picrate, trinitro-m-cresolate, and picrolonate (223-4°, 207-8°, 219°, resp.). The dimethiodide of this base also agreed in optical rotation and m. p. with that of l-nicotine. Späth and Zajic were accordingly the first to isolate l-nornicotine in pure form, having the specific rotation of -88.8°.

Hicks and LeMessurier (18) in 1935 investigated the alkaloid of the Australian plant Duboisia hopwoodii, a plant used by natives to catch emus, by poisoning waterholes, and also chewed on occasion by the natives when real "pituri" was unobtainable. "Pituri," which is plant material chewed by the natives, was found to be a variable product; normally it consists of the leaves of at least two species of Nicotiana, viz, N. excelsior (Black) Black and N. gossei Domin (but not N. suaveolens Lehm.). Because of the variability of the product, the lack of botanical identification, and incorrect chemical deduction, confusion existed in the chemical literature as to the nature of the alkaloid of pituri; some workers reported the presence of nicotine, others denied this. The present work was on authentic D. hopwoodii and indicated the presence of nornicotine.

An alcoholic extract of the leaves led to an alkaloid fraction of b. p. 117° (4.35 mm.), or 266-8° (atm. pres.). It was a colorless oil, gradually browning on exposure to air and light, with a somewhat pungent odor which was definitely sweeter than that of nicotine. It was soluble in water, alcohol, and ether. Various salts were prepared, of which the picrate, picrolonate, and chloroplatinate were obtained crystalline, the latter in orange and yellow forms. The refractive index was 1.5490 to 1.5518 (at 18.6°), compared with 1.529 for nicotine at 16.6°. The specific rotation, $[\alpha]_D^{16}$ -17.5° = +38.59° (d = 1.0757). Molecular weight, by Rast's (camphor) method, was 149.5; by analysis of the orange chloroplatinate, of probable formula $B \cdot 2HCl \cdot PtCl_4$, the combining weight could not be accurately determined, but appeared to have the value 130.1; by analysis of the silicotungstate, $2B_2 \cdot 2H_2O \cdot SiO_2 \cdot 12WO_3$, the value 148.9 was obtained. Carbon and hydrogen determinations on the free base and on the picrolonate (m. p. 252-3°) agreed more closely with nornicotine (m. w. 148) than with nicotine (m. w. 162). $KMnO_4$ oxidation (in collaboration with Späth) gave nicotinic acid, hence the compound was a beta-pyridine derivative, probably d-nornicotine. The ultra-violet absorption agreed with this view; the absorption coefficient (log e = 3.15) was slightly lower than for nicotine (log e = 3.37), but the maximum (2600 A.) was at the same point as for nicotine (2604 A.). For toxicological tests see under Pharmacology (p. 16).

Späth, Hicks, and Zajic (38) in 1935 reported on the examination of the Australian plant Duboisia hopwoodii. The leaves of this plant are used by the natives of Australia as a chewing material and also as an animal poison. Some chemical work had already been done by earlier workers on the chewing material, known as "pituri," but with contradictory results. The reason for the confusion in regard to the alkaloid identity of pituri lay, as pointed out by Hicks, Brücke, and Hueber (17), in the fact that this material was of a variable nature, not always consisting of D. hopwoodii, but frequently being admixed with various

Nicotiana species and with another species of Duboisia. The present investigation on an authentic sample of D. hopwoodii established the presence of d-nornicotine.

From an alcoholic extract of the plant was obtained a main fraction of alkaloid distilling at 117° (3.6 mm.), which proved to be a mixture of d-nornicotine and dl-nornicotine. Analysis indicated the formula $C_9H_{12}N_2$; the molecular weight, found by the camphor method, was 150.2, compared with 148.11 calculated. Other values recorded for this alkaloid are: Density, $d_4^{10} = 1.0757$; refractive index, $n_D^{18.3} = 1.5490$; specific rotation, $[\alpha]_D^{24} = +38.3°$. The ultra-violet absorption was a maximum at 2600 A. U., log e (epsilon) = 3.15. For nicotine the maximum absorption is at 2604 A. U., log e = 3.37. The dipicrate of this alkaloid melted at 191-2° (without bubble formation); the dipicrolonate melted at 252-3°. The base was methylated with formaldehyde and formic acid to nicotine, from which the picrate of m. p. 224° was obtained. The nicotine regenerated from the picrate had in aqueous solution a specific rotation of $[\alpha]_D^{24} = +48.3°$, hence was a mixture of the d and dl forms. Pure l-nicotine when tested under similar conditions (in KOH at low concentration) gave $[\alpha]_D^{24} = -77.78°$. By dividing 77.78 into 48.3 there results 62 percent as the relative amount of d-nornicotine in the alkaloid and 38 percent as the amount of dl-nornicotine. The approximate specific rotation of pure d-nornicotine was then calculated: +38.3 divided by 0.62 = +61.7°. It was realized, however, that this value requires confirmation with the pure d-base. Examination of the methylated base, with respect to the methiodide, trinitro-m-cresolate, and picrolonate, gave results consistent for a mixture of d- and dl-nicotine. A further test made on the Duboisia alkaloid (via benzoylation) proved the absence of nicotine and other tertiary bases.

Hicks (15) in 1936 further investigated the chemistry of the alkaloid of Duboisia hopwoodii. Its methiodide (m. p. 208-9°) was in agreement with the dimethiodide of nicotine (m. p. 208.5-209.5°). Identity had previously been shown by Ehrenstein for the methiodides of l-nornicotine and nicotine (10).

The Duboisia alkaloid was dehydrogenated (Pt-asbestos catalyst) according to procedures used by Wibaut and Overhoff (50) and by Ehrenstein (13). The product, b. p. 194.2° (30 mm.), after recrystallization from a mixture of ether and petroleum ether (large needles), had the m. p. 100-2°; picrate, m. p. 202-3°. These values agreed with those obtained by Ehrenstein for nornicotyrine, 2-[beta-pyridyl] pyrrole. Hence the alkaloid in Duboisia hopwoodii has the nornicotine structure.

Späth, Hicks, and Zajic (39) reported in 1936 that they were able to separate d-nornicotine in practically pure form from the mixed Duboisia base, as the perchlorate. This method had proved successful in isolating pure l-nornicotine from the tobacco bases (46), whereby the value for specific rotation, $[\alpha]_D^{23} = -88.8°$, was obtained. For d-nornicotine from Duboisia was now found $[\alpha]_D^{20} = +86.3°$, which agreed closely in absolute value with that for l-nornicotine. The melting points of the picrate, trinitro-m-cresolate, and picrolonate, of both forms agreed (190-1°, 200°, 252°, resp.).

Späth and Kesztler (43) in 1937, in their study of tobacco bases, investigated the mother liquor remaining after the crystallization of l-nornicotine diperchlorate. The crude base recovered from the liquor had a specific rotation of -33.6°. By means of 1-6,6'-dinitro-2,2'-diphenic acid there was crystallized from methanol solution a salt of which the regenerated base had a specific rotation of $[alpha]_D^{10} = -76.6°$, and hence was still largely l-nornicotine. The base remaining in solution was then treated with the d-form of the above diphenic acid, whereby was obtained a base having $[alpha]_D = +9.2°$. In order to prepare the racemate this slightly positive base was mixed with the calculated quantity of l-nornicotine and the optical inactivity of the mixture was confirmed. A derivative of the racemate was made with 2,4-dinitrobenzoyl chloride. The m. p., 159-60°, was unchanged on mixture with the same derivative of known dl-nornicotine.

There was a possibility that the dl-nornicotine so isolated might have been formed by racemization of l-nornicotine during chemical investigation. Experiments were made by heating l-nornicotine for 48 hours at 100° with 10 percent HCl and with 10 percent KOH. The decrease in rotation amounted to only about 2 percent. Since mild conditions were employed throughout the course of treatment of these alkaloids, it could be assumed that hardly any racemization occurred, and therefore that dl-nornicotine exists as such in tobacco. In a test of a certain German tobacco the alkaloid found therein was practically pure l-nornicotine having $[alpha]_D^{22} = -88.78°$.

By more drastic treatment of l-nornicotine considerable racemization was induced. Thus, by heating with the calculated quantity of H_2SO_4 at 180°, the specific rotation fell after 24 hours to -36.7°, and after 144 hours to -12.6°.

Kovalenko (21) in 1937 reported a study of the alkaloids of N. rusbyi Britt. and Rusby and N. silvestris Speg. and Comes. These plants yielded an alkaloid, or alkaloids, the picrate of which had the m. p. 178-84°. No alkaloid, other than nicotine, was definitely identified, but it was established that another steam-volatile alkaloid was present, which formed an insoluble picrate. It had the character of a secondary amine. (The chief alkaloid in N. silvestris was shown by Smith (37) to be nornicotine.)

Smith (37) in 1937 reported finding l-nornicotine in Nicotiana silvestris, grown in Virginia, in an amount equal to about 95 percent of the total alkaloids, which latter amounted to about 1 percent of the material examined. Associated with the nornicotine was a small quantity of nicotine, which was separated by steam-distillation through a fractionating column. The nicotine was identified by its picrate (m. p. 224°, cor.) and by optical rotation. The base recovered from the residue by ether extraction had the following properties, which identified it as nearly pure l-nornicotine: Sp. gr. 1.07; $[alpha]_D^{20} = -80.0°$; picrate, m. p. 191-2° (cor.); b. p. 270-1°. For comparison, some nornicotine was made from nicotine by $KMnO_4$ oxidation (45). The picrates agreed in melting point. The nornicotine from N. silvestris was methylated with formaldehyde and formic acid (46) to nicotine, the picrate of which had the proper melting point (224°). Smith also established the probable absence of any appreciable quantity of anabasine

in the nicotine-free portion of the N. silvestris alkaloid.

Kostoff and Sarana (20) in 1939 described the results of certain breeding experiments of tobacco. Under the direction of A. A. Shmuck, the nature of the plants was determined in part by the difference between total and volatile alkaloids, and by the m. p. of the picrate. The percentage of total alkaloid was determined by Keller's method, and the volatile alkaloid (which was chiefly nicotine) by Bertrand's method. The nonvolatile alkaloid group could be determined by difference. These differences for most cases of N. tabacum were small, indicating nearly pure nicotine types, whereas in N. silvestris (one of the ancestors of N. tabacum) they were considerable. Hence N. silvestris, according to Shmuck, contains a large percentage of nornicotine. (Smith (37) in 1937 showed that the alkaloid in this species is almost entirely l-nornicotine.)

Hicks (16) in 1940 discussed reasons for the confusion existing over the nature of the alkaloid of Duboisia hopwoodii. He pointed out that earlier workers had probably unknowingly worked on a mixture of D. hopwoodii and Nicotiana excelsior and had therefore found nicotine, whereas in fact the alkaloid of D. hopwoodii is nornicotine.

Markwood (26, 27) in 1940 discovered that a certain strain of ordinary tobacco, N. tabacum, grown in Maryland, contained a high percentage of nornicotine. It was estimated that approximately 95 percent of the total alkaloid (the latter equal to about 0.73 percent of the leaf) was nornicotine and the remaining 5 percent was nicotine. The melting point of the picrate of the unseparated alkaloid fraction was 187-9°, which was indicative of nearly pure nornicotine. After removal of nicotine, the picrate melted at 188.5-190°. The base was methylated with formaldehyde and formic acid, forming nicotine, which was identified by the melting point of its picrate.

The tobacco material examined here was a low-nicotine type. Subsequent unpublished work indicates an association of nornicotine and low-nicotine types. This is in agreement with the opinion of Koenig, cited by Wenusch (47). It is likely that other strains or types of tobacco will also be found to harbor appreciable proportions of nornicotine. A method for readily recognizing a nornicotine type of tobacco has been preliminarily worked out by the writer and awaits further confirmation before publication.

Synthesis

Pictet and Crepieux (29) in 1895 were the first to synthesize nornicotyrine, which is a dehydrogenated nornicotine. By distilling a mixture of beta-aminopyridine and mucic acid the compound N-(beta-pyridyl)pyrrole was formed. This compound underwent rearrangement when heated to a low red heat, forming a low-melting compound (m. p. 72°), a C-(beta-pyridyl)-pyrrole, which was regarded as alpha-(beta-pyridyl)pyrrole(nornicotyrine). The monopicrate, m. p. 182°; chloroplatinate $(C_9H_8N_2 \cdot HCl)_2 \cdot PtCl_4 \cdot 2H_2O$, decomposing at 150°; a mercury compound, m. p. 178-9°; and the methiodide, m. p. 170-1°, were described.

Chichibabin and Bylinkin (6) in 1923 prepared a C-(alpha-pyridyl)-

pyrrole, starting with alpha-aminopyridine and mucic acid, which were reacted in the presence of Al_2O_3 as a contact substance for splitting out H_2O. By passing the N-(alpha-pyridyl)pyrrole through a slightly glowing tube they effected rearrangement into an isomeric C-(alpha-pyridyl)pyrrole, which they identified as alpha-(alpha'-pyridyl)pyrrole (alpha-nornicotyrine), m. p. 87-8°.

Wibaut and Dingemanse (49) in 1923 followed along the line described by Pictet and Crepieux (29) but started with alpha-aminopyridine. The product obtained by reaction with mucic acid, and subsequent thermal rearrangement of the N-(alpha-pyridyl)pyrrole, was a mixture of two isomeric C-(alpha-pyridyl)pyrroles; the main product had the m. p. 90°, while the other isomer had the m. p. 132°. One of these compounds was alpha-nornicotyrine, but which one was not then determined. The compound of 90° m. p. was identical with the pyrrole (m. p. 87-8°) reported by Chichibabin and Bylinkin (6).

Wibaut (48) in 1926 established the structure of the two isomeric C-(alpha-pyridyl)pyrroles previously prepared by Wibaut and Dingemanse (49). By the reaction of ethyl phenylacetate, chloroacetaldehyde, and NH_3 was obtained a C-(alpha-pyridyl)pyrrole which could have only the alpha-alpha structure. This pyrrole, m. p. 87.5-88.2°, was identical with the pyrrole of 90° m. p. of Wibaut and Dingemanse, and hence the latter compound was alpha-nornicotyrine (alpha-(alpha'-pyridyl)pyrrole). The other pyrrole (m. p. 132°) was therefore beta-(alpha'-pyridyl)pyrrole.

M. and M. Polonovski (31) in 1927 described a general method for dealkylating tertiary amines to secondary amines, chief amoung such being the tropine alkaloids. The method was then extended to include nicotine, whereby nornicotine was claimed to be formed (32, 33). The method consisted in treating nicotine oxide (the "oxynicotine" of Pinner and Wolffenstein, Ber. 24, 61-7, 1891) with either acetic or benzoic anhydrides to form the corresponding acyl derivative, which was then saponified, preferably with alcoholic KOH, to nornicotine. The intermediates, acetyl-nornicotine and benzoyl-nornicotine, were thick oils. Nornicotine, best purified as the chloroaurate, was an oil, very soluble in water, from which it was separated by strong alkali, and was readily extracted by ether. The freshly distilled base, b. p. 150-155° at 30 mm., was colorless, but rapidly darkened and resinified in air; it was difficultly volatile with steam, of an odor recalling nicotine. It had the specific rotation, [alpha] = -20° (C = 3.8, in methanol). They prepared the dipicrate, m. p. 135°; chloroaurate, $C_9H_{12}N_2 \cdot 2HCl \cdot 2AuCl_3$, m. p. 210-2°; nitroso derivative, an oil extractable with ether; and an oily phenyl isocyanate derivative. From later, more trustworthy work, it is seen that the nornicotine obtained here was at best very impure.

Von Braun and Weissbach (5) in 1930 confirmed the inadequacy of the Polonovski procedure, and proceeded along a similar line with better results.

They reacted nicotine with benzoic or with hydrocinnamic acids (the latter was preferable), thus obtaining the acyl derivative, which was then saponified to nornicotine. A secondary reaction in the acylation resulted in the opening of the pyrrolidine ring with the formation of a metanicotine derivative. By treatment of the crude reaction product

with HBr a separation was effected, and at the same time the hydrocinnamoyl-nornicotine was hydrolyzed to nornicotine, which was removed in pure condition with ether. The yield was about 20 percent, based on hydrocinnamic acid, but less on the nicotine, which was used in excess.

The nornicotine obtained had the following properties: B. p., 266-7° at atmospheric pressure; 139-40° at 12 mm. It was colorless, stable in air (no darkening or resinifying as with the Polonovski product), miscible with water, strongly basic, of piperidine-like odor. Density, $d_4^{19} = 1.044$. Specific rotation, [alpha] = -5.5°, but this value was believed to be lower than the maximum rotation because of partial racemization. The picrate was obtained fairly pure by recrystallization from alcohol; m. p. 188-90°. Purer than the picrate was the finely crystalline picrolonate, from alcohol; m. p. 239-40° (sharp). The hydrochloride could be obtained only as an oil. The chloroplatinate was obtained as small, dark-red crystals, darkening at 270° and decomposing at 295°. The chloroaurate was obtained as yellow crystals, m. p. 217°.

Nitroso-nornicotine was readily formed by reaction of the base with $NaNO_2$ in HCl solution; it was a yellow, viscous oil of b. p. 190-2° at 0.5 mm., miscible with water but separated therefrom by saturation with K_2CO_3 and extracting with ether, or better, methylene chloride. The picrate, HCl salt, and Au salt were oily. The Pt salt formed fine crystals of m. p. 190°. The monomethiodide was well crystallized, m. p. 144°. The nitroso derivative was converted into nornicotine by treatment with excess of strong HCl. By nitriting a mixture of nicotine and nornicotine a separation of these two bases can be effected, thus: The product is nitrited, then fractionated, whereby the lower-boiling unchanged nicotine is separated, and the nitroso-nornicotine is converted as above. [Such conversion and regeneration of nornicotine, however, probably results in partial racemization.]

Nornicotine readily formed an acetyl derivative with acetic anhydride. This derivative was a viscous oil; b. p. 212-4° at 12 mm.; specific rotation, $[\alpha]_D^{20} = -3.24°$ (in benzene). It formed a picrate, m. p. 151°; an oily Au salt; a Pt salt which decomposed at 245°; and a methiodide, colorless needles, m. p. 201°.

Nornicotine formed a colorless, crystalline carbamide with cyanic acid, which was nornicotinyl carbamide, $C_{10}H_{13}ON_3$, m. p. 164-6°. Its Pt salt, small red crystals, darkened at 250° and decomposed at 270°. The picrate was oily. Nornicotine also formed a colorless, crystalline derivative with phenyl isothiocyanate, of composition $C_{16}H_{17}N_3S$ and m. p. 171°.

By the action of ethyl iodide on nornicotine, N-ethyl-nornicotine was made, of b. p. 127-8° at 12 mm. The HCl salt was a hygroscopic solid; the Au salt, yellow crystals which decomposed at 203°; the picrate, m. p. 174-6°. By similar treatment of nornicotine with allyl bromide was formed N-allyl-nornicotine, a colorless liquid, b. p. 136-7° at 12mm. It formed a picrate, m. p. 180-2°; a Au salt, decomposing at 145-8°; a Pt salt, orange crystals, darkening at 230° and decomposing at 255°.

Späth, Marion, and Zajic (45) in 1936 effected the demethylation of nicotine into nornicotine in two ways. A. By treatment of nicotine with $KMnO_4$ a 0° in aqueous solution a partial demethylation occurred. The crude mixed basic product was dissolved in ether and fractionally extracted with 0.1 N HCl saturated with NaCl, whereby the nornicotine was removed with only a small admixture of nicotine. The nicotine was then expelled by vacuum distillation with water. The crude product was purified by repeated recrystallization of the picrate, which was finally obtained pure with a melting point of 191°. The picrate was decomposed with HCl, the free base recovered and distilled. There was thus obtained, from 6.0 g. of nicotine, 0.41 g. of nornicotine. Specific rotation, $[alpha]_D^{20} = -76.1°$; by crystallization as the perchlorate the rotation was increased to $[alpha]_D^{20} = -83.2°$. [Calculates to a density, $d^{20} = 1.070$.] The picrolonate, m. p. 252°, and the trinitro-m-cresolate, m. p. 200° were made. B. The second method employed by these workers for demethylating nicotine consisted in treatment with silver oxide. This reaction dates back to Blau (Ber. 27, 2535-9, 1894), who thereby prepared nicotyrine, a dehydrogenation product of nicotine, but did not report the formation of nornicotine. The crude reaction product was fractionated as before. From 40 g. of nicotine there was obtained 3.9 g. of nornicotine dipicrate, m. p. 190-191°. Before conversion to picrate the base had a specific rotation of -40°; after purification via the picrate it showed $[alpha]_D^{20} = -88.8°$ ($d_4^{20} = 1.070$).

Craig (7) in 1933 synthesized nornicotine, and from it nicotine, by a series of aggregating steps starting with pyridine. Hence this method, while lengthy, represents more truly a synthesis than does the demethylation of nicotine. Pyridine was sulfonated to sodium beta-pyridine sulfonate and the latter converted with NaCN to nicotinic acid nitrile. The nitrile was then reacted with the Grignard reagent made from gamma-bromo-propyl ethyl ether, whereby was formed beta-pyridyl-gamma-ethoxypropyl ketone, which was a new compound. From this ketone was formed the oxime with hydroxylamine. The oxime was reduced to the amine, 1-[beta-pyridyl]-1-amino-4-ethoxybutane, which was dealkylated with HBr to the hydroxy compound. Ring closure to make the pyrrolidine ring followed, and by addition of KOH a basic oil separated from which was obtained an oil distilling at 139-140° (12 mm.). The properties of this oil agreed throughout with those reported by von Braun and Weissbach (5) for nornicotine, and similarly the picrate and phenylthiourea compounds were in agreement. Methylation with CH_3I to racemic nicotine followed. The author noted that nornicotine is a stronger base than nicotine. The foregoing process represented a complete new synthesis from pyridine of the two bases in racemic form.

Craig (8) in 1934 by a similar procedure prepared so-called alpha-nornicotine and alpha-nicotine, in which linkage to the pyridine ring is in the alpha position instead of the beta position. The alpha-nornicotine was described as a rather pleasant-smelling oil, soluble in water and in organic solvents in all proportions. The picrate melted at 166°. A phenylthiourea derivative was made but could not be obtained pure.

Späth and Kesztler (41) in 1936 resolved synthetic dl-nornicotine prepared by the method of Craig (8) into the two optical antipodes. Whereas Pictet and Rotschy (Ber. 37, 1225-35, 1904) were able to resolve

dl-nicotine by means of tartaric acid, this acid proved unsuitable for nornicotine, and resort was had successfully to the optically active acid, 6,6'-dinitro-2,2'-diphenic acid, which gave well-crystallized salts with the several tobacco bases. The preparation of this acid and its resolution into d- and l-forms through the quinine salt were discussed. The dl-nornicotine was first treated in methanol solution with l-6,6'-dinitro-2,2'-diphenic acid; crystals of l-nornicotine l-dinitrodiphenate were obtained. The base recovered from the latter by decomposition with HCl first had a rotation, $[\alpha]_D^{19} = -48.9°$; after purification through the perchlorate it had $[\alpha]_D^{17} = -87.85°$. The mother liquor, on treatment with the d-diphenic acid, gave crystals of d-nornicotine-d-dinitrodiphenate, the recovered base of which first had a rotation, $[\alpha]_D^{17} = +48.0°$, and after purification as the perchlorate had $[\alpha]_D^{18} = +86.08°$.

For l-nornicotine diperchlorate so prepared, $C_9H_{14}O_8N_2Cl_2$, m. p. 183-6°, $[\alpha]_D^{18} = +13.6°$ (in water; c = 5.28). For the diperchlorate of natural l-nornicotine, $[\alpha]_D^{18} = +13.4°$ (in water, c = 5.23). For d-nornicotine diperchlorate, $[\alpha]_D^{16} = -12.98°$ (in water, c = 5.24).

Späth and Kainrath (40) in 1938, in their work on the simplification of the classical Pictet nicotine synthesis, prepared the compound 1-(3'-pyridyl)pyrrole from 3-aminopyridine and mucic acid. This pyrrole by thermal treatment at 700° rearranged into two isomeric pyrroles, of which one was 2-(3'-pyridyl)pyrrole (nornicotyrine), m. p. 97° (picrate, m. p. 200-2°); the other isomer was 3-(3'-pyridyl)pyrrole. Separation was effected by repeated crystallization of the free bases and their picrates. Nornicotyrine was reduced with hydrogen and Pd-sponge as catalyst to dl-nornicotine (dipicrate, m. p. 194°). The crude hydrogenation product was also methylated with formaldehyde and formic acid to dl-nicotine.

Lions and Ritchie (22) in 1940 published a new synthesis of nornicotyrine, 2-(3'-pyridyl)pyrrole, in order definitely to confirm its constitution. It was synthesized from ethyl nicotinylacetate, $NC_5H_4COCH_2CO_2C_2H_5$, ethoxy ethylenedichloride, $CH_2ClCHClOC_2H_5$, and strong NH_3. The purified product, nornicotyrine, was isolated in the form of needles, m. p. 98-9°, which gave a blue fluorescence in a mixture of benzene and petroleum ether (picrate, m. p. 203-4° (d.)). This type of synthesis, involving NH_3, represents a departure from most former modes but is similar to the synthesis of alpha-nornicotyrine, employed by Wibaut (48) in 1926.

Analytical Determination

Qualitative tests for nornicotine are based upon such factors as the appearance and melting point of salts, e. g., picrate 191-2°, 2,4,6 trinitro-m-cresolate 200°, picrolonate 252°, urea 167-70°, phenylthiourea 176-7°, and chloroaurate 217°.

Methylation to nicotine, with identification of the latter, is valuable evidence of nornicotine.

The optical rotation and other physical properties are also valuable means of identification.

The quantitative determination of nornicotine has not been fully investigated. It may be said, however, that any methods applicable to nicotine (with due regard to the difference in volatility with steam) are also applicable to nornicotine. The chief problem most likely to be encountered is the quantitative separation of nornicotine and nicotine as they occur in tobacco.

Von Braun and Weissbach (5) in 1930 pointed out that a separation of nornicotine from nicotine could be effected by forming the nitroso derivative of nornicotine with KNO_2 in HCl solution; nicotine was not changed thereby. They then fractionally distilled the isolated bases and obtained nicotine as the lower-boiling fraction. [This method may be satisfactory for a quantitative determination of nornicotine, but it is open to objection in the preparation of l-nornicotine because subsequent regeneration of nornicotine from the nitroso compound by means of strong HCl may result in racemization.]

P. Koenig (19) in 1934 observed that the distillates of certain tobaccos gave picrates of melting point departing considerably from that for pure nicotine (218-222.5°). These picrates melted at 214°, 205°, 193°, and even 173°; the depression in melting point was attributed to foreign bodies, of which the chief one was nornicotine. He described a method for quantitatively separating these bases, by virtue of their difference in basicity and in volatility with steam. A distillation from MgO solution yielded only the nicotine in the distillate, while the NaOH distillation yielded both alkaloids. This was explained by the fact that nornicotine, being the stronger base, was less readily liberated from its salts, and also that it was less volatile with steam. The bases in the respective distillates were precipitated with picric acid, and the picric acid content of the picrates was determined by titration with NaOH. [Note: This separation is only approximate, and it favors a high value for nicotine, as nornicotine is volatile enough to distil over partially from MgO solution.]

Pharmacology

Dingemanse, Laqueur, and Wibaut (9) in 1926 reported on the pharmacology of certain pyridine and pyrrole derivatives. Among them was alpha-nornicotyrine (alpha-(alpha'-pyridyl)pyrrole), m. p. 90°. A frog injected with 1 cc. of a 1-percent solution of alpha-nornicotyrine showed symptoms of paralysis. As an anesthetic this compound was about twice as active as novocaine. The general conclusion reached from this and other tests was that the alpha-pyridine compounds have about the same degree of physiological activity as the beta-pyridine compounds. (This conclusion, however, is not borne out by the tests of other investigators.)

The first information concerning the toxicity of nornicotine comes from A. Bergwall, whose report of pharmacological tests was cited by Ehrenstein (13) in 1931. It was the latter's nornicotine, isolated from tobacco, which was tested, and this it should be noted was not

pure l-nornicotine but a mixture of the l- and dl-forms (approximately 20 percent l- and 80 percent dl-nornicotine).

Tests on the contraction of frog muscle showed nornicotine to have only one-tenth the activity of nicotine. Blood pressure tests on cats (injection in the Vena jugularis) showed that nornicotine, like nicotine, causes a rise in arterial pressure which is accompanied by irregular heart action, but the effect was weaker than that produced by nicotine. It was difficult to give numerical evaluation to tests of this kind, as repeated injections diminished the effects. Nornicotyrine (2-[beta-pyridyl]-pyrrole), on the other hand, caused a lowering of blood pressure, but the action was relatively weak.

Macht and Davis (23) in 1934 reported toxicity tests on the following compounds, which were prepared by L. C. Craig:

l-beta-nicotine
dl-beta-nicotine
dl-beta-nornicotine
dl-alpha-nicotine
dl-alpha-nornicotine
(l-beta-Nornicotine, the form naturally occurring in tobacco, was not included.)

The tests embraced growth studies on seedlings of Lupinus albus L., and mortality studies on tadpoles, goldfish, water turtles, land turtles, white mice, white rats, guinea pigs, and cats.

All five compounds were toxic, but the order of toxicity varied with the different test objects. In nearly all cases l-beta-nicotine (natural nicotine) was the most toxic. The beta compounds without exception were more toxic than the alpha. In general dl-beta-nornicotine was more toxic than dl-beta-nicotine, but there were exceptions. As between dl-alpha-nicotine and dl-alpha-nornicotine, the order of toxicity was about equally divided.

A typical picture of toxicity, showing the effect of intravenous injection of cats, in terms of mg. of compound per kg. of cat for lethal dose, is given in the following set of values (the order of compounds is that given above): 1.3, 2.0, 0.9, 6.1, 13.1.

Macht and Davis (24) in 1935 made a special report on the toxicity of the several compounds tested previously (23). The test here was confined to inhibition of root growth of seedlings of Lupinus albus. The data and conclusions of the previous article were substantiated. In addition, new data were given on the effect of combinations of these bases. The results showed that certain combinations gave simple additive effects, agreeing with the calculated summation, while others produced a synergistic (greater than the calculated) effect, and still other combinations were antagonistic.

Hicks and LeMessurier (18) in 1935 investigated the toxicological behavior of the alkaloid of Duboisia hopwoodii, which was nornicotine, roughly in 1:1 ratio of the d- and dl-forms. The m. l. d. for rats (peritoneal injection) was 0.0017 g.; the m. l. d. of nicotine was

0.0045 g.; hence the Duboisia alkaloid was about 2-1/2 times as toxic as nicotine. The action on the isolated perfused mammalian heart was similar to that of nicotine. Intravenous injection into the intact animal (rabbit) caused a rise of blood pressure similar to that given by adrenaline, followed by paralysis of the vagus. This effect was similar to that produced by stimulation of the splanchnic ganglia by nicotine. The action on isolated frog's gastrocnemius preparation was similar to that of nicotine. It was noted that the symptoms of poisoning in the rat were distinct from those produced by nicotine, although death in both cases was due to respiratory failure. The Duboisia plant is also known to be very toxic to camels, as one mouthful of the bush is fatal to these animals.

Hicks, Brücke, and Hueber (17) in 1935 reported more completely on the pharmacology of d-nornicotine, which was isolated from Duboisia hopwoodii. Blood-pressure experiments on cats were conducted, and the action on peripheral ganglia was studied, both with reference to heart ganglia (isolated frog heart) and to the ganglion cervicale supremum (cat). The action on isolated frog muscle (musc. rectus abdominis) and on the posterior extremities of a dog were also studied. The conclusions reached were that the action of d-nornicotine on blood pressure, respiration, and vasomotor centers, as well as on peripheral vagal and sympathetic ganglia and on the heart, is not different from that of nicotine. The isolated frog muscle was somewhat more sensitive to d-nornicotine than to nicotine, but the difference was only slight.

Richardson, Craig, and Hansberry (34) in 1936 summarized the toxic action of a group of N-heterocyclic compounds upon the bean aphid, Aphis rumicis L. The compounds were applied in 0.25 percent sodium oleate solution. The concentrations required for 50 and 100 percent mortalities of the insect were:

Compound	50 percent net mortality mg. per 100 cc.	100 percent net mortality mg. per 100 cc.
l-beta-nicotine	49	1,185
dl-beta-nornicotine	45	490
dl-alpha-nicotine	1,496	10,960
dl-alpha-nornicotine	1,514	10,470
dl-beta-nicotine	96	1,259
anabasine	5	166

The results show the marked superiority of the beta compounds. Anabasine stands out as the most toxic aphicide. There was no great difference between the comparable methyl- and nor-forms. Natural nicotine was about twice as toxic as its racemic isomer. Although l-beta-nornicotine, the alkaloid occurring in tobacco, was not included in this study, the racemic form of beta-nornicotine was shown to be somewhat more toxic than natural nicotine, and hence l-beta-nornicotine quite likely would have a toxicity of the same order. It should be borne in mind that the results reported here apply only to the bean aphid and that the degree and order of toxicity can be different for other insects. This work represents the first insecticide investigation reported on nornicotine.

Wenusch (47) in 1936 published an interesting account of the toxicity of l-nornicotine as it relates to the smoking of tobacco. Cigarettes made of a nornicotine tobacco were smoked by intermittent puffs, and the smoke was caught in dilute sulfuric acid. The strongly alkaline liquid was exhaustively steam-distilled, and the picrate of the alkaloid was formed in the distillate. Since nornicotine dipicrate is more soluble in water and in alcohol than is nicotine dipicrate, it was possible to effect a separation of these two bases by fractional crystallization of the picrates. Compared with the amount of nornicotine in the original tobacco, the amount in the main smoke stream was quite small; about 25 percent of nicotine passes into the smoke by intermittent smoking but the corresponding percentage of nornicotine is much less.

In the soluble picrate fraction, beside one of m. p. 217-8°, there was obtained a picrate that blackened at 150°, sublimed in drops, melted at 192-4°, and when made alkaline smelled strongly like myosmine (mousy odor) but was not myosmine. A picrate of the same properties was prepared from nornicotine by $KMnO_4$ oxidation. Since this picrate could not be obtained directly from tobacco, it must owe its origin to air-oxidation of nornicotine on smoking. It appeared to be much less toxic than nicotine.

l-Nornicotine was physiologically less active than l-nicotine, as revealed by tests on the contraction of leech muscle. A solution of 1:300,000 of l-nicotine produced approximately the same degree of contraction as a 1:60,000 solution of l-nornicotine, hence the activity was roughly one-fifth.

The conclusion reached was that the presence of l-nornicotine in tobacco is toxicologically of minor importance since it is less toxic than nicotine and passes over into the smoke to a much less degree than nicotine.

Hansberry and Norton (14) in 1940 reported on aphicidal (Aphis rumicis) tests with l- and d-nicotines and l-, d-, and dl-nornicotines. The l-nicotine was obtained pure by the method of Ratz (Monatsh. 26, 1241-52, 1905); [alpha] =-168.90°. The d-nicotine was crystallized as the l-tartrate from racemized nicotine, prepared by heating natural nicotine with H_2SO_4. The l-nornicotine was isolated from N. silvestris grown at Ithaca, N. Y.; the plant contained approximately 1.4 percent crude alkaloids, of which 57 percent was nicotine and 43 percent nornicotine. The purified l-nornicotine had a specific rotation, [alpha] = -82°. The d-nornicotine was the base prepared from Duboisia hopwoodii and was furnished by C. S. Hicks of Australia. The dl-nornicotine was prepared from nicotine by the method of von Braun and Weissbach (5); the rotation was not determined; the picrate melted at 191-191.5°.

The compounds were applied in 0.25 percent sodium oleate solution. The results are shown in the following table:

Mean percent mortality of Aphis rumicis L.

Material	Concentrations used, percent					
	0.005	0.02	0.05	0.2	0.4	2.0
l-nicotine	8	32	80	87	100	
d-nicotine			28	45	90	100
l-nornicotine	16	63	98	100		
d-nornicotine	16	45	65	100		
dl-nornicotine	13	37	90	100		

It is apparent that d-nicotine was substantially less toxic than any of the other alkaloids. All the nornicotines were more toxic than natural (l-) nicotine. l-Nornicotine was doubtfully more toxic than the d- or dl-forms. No pronounced difference existed between the d- and l-forms of nornicotine. The data indicate that extracts of Nicotiana silvestris and Duboisia hopwoodii may be better insecticides than nicotine, toward some insects.

The results of the tests with aphids indicate that nornicotine should be tested as an insecticide against other species. It may also have other uses, such as a vermifuge for poultry and other animals, especially if the nornicotine, when used for this purpose, proves to be less toxic to the host than is nicotine.

Patents

U. S. patent 2,219,287, dated October 29, 1940, to Robert B. Arnold (4), assignor to Tobacco By-Products and Chemical Corporation, specifies the group anabasine, nornicotine, and nicotine in combination with a base-exchange polysilicate, as a parasiticidal spray composition.

Reviews and Popular Accounts

Marion (25) in 1938 presented a review of the tobacco alkaloids, which included a discussion of nornicotine.

Späth and Kuffner (44) in 1939 presented a comprehensive review on the entire subject of tobacco alkaloids, of which nornicotine is one.

Popular accounts of Markwood's discovery of nornicotine in Maryland tobacco appeared in Science News Letter (3), Science Digest (2), Modern Medicine (1), and in newspapers, such as the New York Times (Sept. 8, 1940) and Buffalo Evening News (Oct. 16, 1940).

Summary

Nornicotine is a colorless liquid alkaloid which occurs in the Nicotiana species tabacum L. and silvestris Speg. and Comes, and in Duboisia hopwoodii F. Muell. It probably also occurs in other incompletely investigated species of Nicotiana. In chemical composition it

is 2-(3'-pyridyl)pyrrolidine, $C_9H_{12}N_2$, and differs from nicotine, to which it is closely related in chemical structure and physiological action, by the presence of an NH instead of an $N \cdot CH_3$ group.

Nornicotine appears to be more stable than nicotine, has a higher boiling point, and is less volatile with steam.

Pharmacological tests indicate that in general it is less active than nicotine toward warm-blooded animals, but that toward insects (as judged by behavior with Aphis rumicis L.) it is equally toxic, perhaps even superior. This conclusion is only provisional, however, as very few insecticidal tests have been made.

The prospects for a supply of nornicotine are excellent, since a fairly rich source of it has been found in a domestic tobacco. From the insecticidal point of view it deserves thorough testing by entomologists. It may also have other applications, such as a vermifuge for poultry and animals.

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